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Neurodevelopmental outcome in very low birth weight infants with pathological umbilical artery flow

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Neurodevelopmental outcome in very low birthweight infants with pathological umbilical artery flow

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ABSTRACT

Objective To assess neurodevelopmental outcome during toddlerhood in very low birthweight (VLBW) infants with absent or reverse end-diastolic flow (AREDF) in the umbilical artery (UA) during pregnancy.

Design Retrospective cohort study with matched control group.

Setting Tertiary perinatal centre.

Patients and outcome measures We compared longitudinally collected data on neonatal and neurodevelopmental outcomes among 41 infants born in our institution from 1997 to 2010 with birth weight <1500 g and UA AREDF and 41 infants with prenatally normal UA Doppler parameters matched for gestational age, birth weight, sex and year of birth. We evaluated neurodevelopmental outcome at a median (range) corrected age of 23.3 (10.1–29.6) months using the Bayley scales of infant development, 2nd edition (BSID-II), and neurological examination.

Results The mental development index in UA AREDF children (median (range) 84 (49–116)) was significantly lower than in controls (median (range) 91 (62–140)), including after adjustment for confounders. Intergroup differences in psychomotor development index (PDI; BSID-II) and the rate of cerebral palsy or minor neuromotor dysfunction were non-significant.

Conclusions VLBW infants with UA AREDF have a higher risk of poorer mental development during toddlerhood than controls matched for gestational age, birth weight, sex and year of birth. UA AREDF may be considered a prenatal predictor of poorer mental development in this population. Long-term follow-up studies with larger cohorts are needed to better evaluate the impact of this prenatal factor on later neurodevelopment.

What is already known on this topic?

- Pathological umbilical artery Doppler parameters are evidence of placental insufficiency and often synonymous with intrauterine growth restriction.
- Absent or reverse end-diastolic flow in the umbilical arteries carries high perinatal and neonatal morbidity and mortality.

What this study adds?

- Mental development is significantly impaired in very low birthweight toddlers with prenatally absent or reverse end-diastolic flow in the umbilical arteries compared with gestational age, birth weight, sex and year of birth matched controls.
- Absent or reverse end-diastolic flow in the umbilical arteries seems to be an independent prenatal predictor of adverse neurodevelopmental outcome in very low birthweight infants.

INTRODUCTION

Placental dysfunction comprising a reduction in functional villi and small blood vessels may increase placental resistance[1 2] and impair uterine artery blood flow.[3] A compensatory mechanism increases blood flow in the fetal middle cerebral arteries (MCA), indicating redistribution to the brain.[4] Placental dysfunction can also be detected by a decrease in end-diastolic flow (EDF) velocity in the umbilical artery (UA). If placental resistance keeps rising, it causes absent EDF (AEDF) or even reverse EDF (REDF) in the UA.[5 6] These abnormal Doppler parameters are strong indicators of placental insufficiency or, in most cases, of intrauterine growth restriction (IUGR).[7] While IUGR is associated with adverse perinatal and neurodevelopmental outcomes,[8 9] absent or reverse EDF (AREDF) in the UA and REDF in particular carry high perinatal and neonatal morbidity and mortality.[10 11] Infants with UA AREDF during pregnancy may experience neonatal complications such as respiratory distress syndrome, bronchopulmonary dysplasia, necrotising enterocolitis, anaemia and cerebral bleeding.[12 13] However, extensive descriptions of perinatal and neonatal outcome after AREDF[8 9 14 15] have tended to overshadow those of the long-term neurodevelopmental outcome of this pregnancy complication.[16–18]

Our aim was to investigate the association between UA AREDF and neurodevelopmental outcome in very low birthweight (VLBW) infants at corrected age (CA) of 2 years compared with a matched group of controls with normal antenatal Doppler parameters during pregnancy.

METHODS

Subjects

We undertook a retrospective analysis of all infants with a prenatal Doppler diagnosis of UA AREDF,

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weighing <1500 g at birth, and born between February 1997 and April 2010 at Zurich University Hospital (a tertiary referral centre). Exclusion criteria were multiple pregnancy, congenital malformation, chromosomal aberration and incomplete Doppler or clinical maternal data. We individually matched this index group by gestational age (GA; ±1 week), birth weight (±300 g), sex and year of birth (±1 year) with a control group of singletons born in our institution and possessing normal antenatal Doppler values and available 2-year outcome data. We determined GA from the known first day of the last menstrual period or sonographic first-trimester crown–rump length,[19] corrected to the latter if the difference between these two parameters exceeded 5 days. We defined small for GA (SGA) as birth weight <10th centile[20] and major brain injury by cerebral ultrasound as grade ≥3 intraventricular haemorrhage[21] and/or cystic periventricular leukomalacia.[22] A requirement for additional oxygen at $36^{0/7}$ weeks' postmenstrual age defined bronchopulmonary dysplasia.[23] Retinopathy of prematurity (ROP) was defined using International Committee criteria.[24] Proven sepsis (positive blood or cerebrospinal fluid culture) was defined as previously described.[25] We sourced the following sociodemographic variables from the clinical records: maternal age, parity, ethnicity and socioeconomic status (SES),[26] estimated using a validated 6-point scale of maternal education and paternal occupation, ranging from 2 to 12 (the higher the score the lower the status). We also evaluated maternal outcome, for example, preeclampsia, histopathological chorioamnionitis and delivery mode.

Prenatal Doppler examination

Doppler studies were performed by sonographers trained in maternofetal medicine. Waveforms were obtained on pulsed wave Doppler ultrasound systems (Acuson 128XP10 and Allegra, Siemens Medical Solutions, D-91052 Erlangen, Germany; Voluson 730 Expert, GE Healthcare, USA) after identifying the free-floating portion of the UA by colour flow imaging. The high-pass filter was 50 Hz. Doppler parameters included flow measurements in the UA, MCA and uterine arteries.

Neurodevelopmental outcome assessment

Comparison of neurodevelopmental outcome at CA of 2 years between index and control groups was the primary endpoint. All infants were prospectively examined as part of the routine Swiss follow-up assessment of prematurity at the Zurich Development Centre, Zurich University Infants' Hospital, at CA 12–24 months, that is, the age the infant would be if it had been born on its due date, and neurodevelopmental outcome was determined. Assessment by experienced developmental paediatricians blinded to prenatal UA flow comprised Bayley scales of infant development (2nd edition) and clinical and standardised neurological examination.[27] Expected means and SDs for the mental and psychomotor development indices (MDI and PDI) were 100±15. MDI and/or PDI <70 indicated neurodevelopmental impairment. Standardised neurological examination addressed active muscle power, muscle tone, deep tendon reflexes and the cranial nerves. Cerebral palsy (CP) was defined as a permanent non-progressive movement and posture disorder, causing activity limitations due to non-progressive disturbances of the developing fetal or infant brain,[28] and was graded according to the modified gross motor function classification system (GMFCS).[29] Minor neuromotor dysfunction was defined as a spectrum of motor disorders other than CP, including abnormal tone and/or reflexes, and clumsy fine and/or gross motor performance. Vision and hearing were assessed either by direct examination or caregiver report.

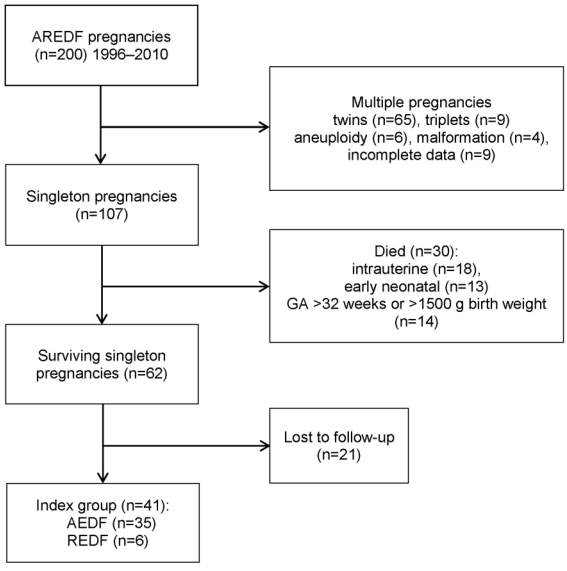
Statistics

Statistical analyses were performed using SPSS V.20.0 (SPSS, Chicago, USA). We used Fisher's exact test, independent t tests and the Mann–Whitney U test to compare frequencies of normally and non-normally distributed variables between index infants and controls. Comparison analyses of outcome measures were adjusted for baseline characteristics that differed significantly between the two groups using multivariate regression analysis for the perinatal and demographic variables. Continuous dependent variables were MDI and PDI; binary variables were MDI <70, PDI <70, CP, minor neuromotor dysfunction, visual and hearing problems and ongoing physical or occupational therapy. We also analysed the association between continuous MDI and PDI and known outcome predictor variables as follows: in step 1, we included the predictors GA, sex, antenatal corticosteroids, bronchopulmonary dysplasia, sepsis, major brain injury, ROP >stage 2 and SES in the model equation one at a time (univariate); in step 2, we performed multivariate regression analysis to evaluate the independent effect of these variables on the outcome measures based on their statistical importance in the univariate analyses. We used the Kolmogorov–Smirnov goodness-of-fit statistic to test for normal distribution. A significance level of <0.05 was applied throughout.

The cantonal ethics committee approved the study protocol (KEK-ZH-No. 2012 0182). Written consent was obtained from all the women involved.

RESULTS

Of the 200 pregnancies complicated by AREDF observed during the study period, 93 (47%) were excluded from the analysis because of multiplicity (65 twins, 9 triplets), aneuploidy (n=6), congenital malformation (n=4) and missing data (n=9). Of the remaining 107 singleton pregnancies, 18 infants died in utero, 13 infants with a median (range) GA of 24 (23.0–25.1) weeks died during the first week of life and 14 infants were born with birth weight >1500 g. Of the remaining 62 infants, 21 were lost to follow-up. The index group, thus, comprised 41 infants, 22 (54%) of whom were male. Median (range) GA was 29.9 (24.9–35.0) weeks and birth weight 910 (400–1460) g. UA AEDF was present in 35 pregnancies and REDF in six (figure 1).



AEDF, absent end-diastolic flow; GA, gestational age; REDF, reverse end-diastolic flow

Figure 1 Index group selection and exclusion criteria.

Differences in GA, birth weight, sex, major brain injury, sepsis and SES between study infants and those lost to follow-up were non-significant (p>0.05). Differences in antenatal and neonatal characteristics between index and control groups were also non-significant apart from higher rates of SGA (p=0.01) and antenatal corticosteroids for lung maturation (p=0.04) in AREDF infants (table 1). Comparison of sociodemographics (table 1) showed that mothers of AREDF infants were significantly younger than those in the control group (p=0.01).

Neurodevelopmental outcome

At assessment at median 23.3 months' CA, AREDF infants and controls were similar in median age, body weight, length and head circumference (table 2). Median MDI was significantly lower in AREDF infants than in controls (p=0.005), and remained so after adjustment for antenatal corticosteroids, SGA and maternal age (p=0.03). Similarly, the proportion of infants with MDI <70 was significantly higher in the index group (p=0.01, adjusted p=0.004). We observed no other intergroup difference concerning the other measured outcome parameters.

Univariate regression analysis revealed significant positive associations between MDI and GA (p=0.02) and higher SES (p=0.03). No significant association was identified between PDI and any predictor. Multivariate regression analysis revealed an independent negative association between AREDF and MDI (p=0.048; table 3).

The AREDF group comprised two infants with bilateral spastic CP (GMFCS level 1: 18.3 months' CA; level 2: 20.5 months' CA), and the control group comprised two infants with unilateral spastic CP, and one infant with dyskinetic CP (all GMFCS level 1: 19.3, 23.8 and 21.8 months' CA) (table 2).

Comparison of neurosensory outcome revealed no significant intergroup difference in the rate of visual or auditory problems. Five AREDF infants (12%) with visual problems had myopia, pendular nystagmus, cloudy peripheral cornea (n=1 each) and convergent squint (n=2); three controls (7%) had myopia (n=2) and convergent squint (n=1). Of the two AREDF infants (5%) with hearing problems, one needed a cochlear implant and the other had minor unilateral hearing loss.

At assessment, 14 AREDF infants (34%) and 12 controls (29%) had ongoing physical therapy, and one infant per group (2%) was having occupational therapy.

DISCUSSION

Our study compared outcome data at about 2 years between 41 VLBW toddlers with antenatal UA AREDF and 41 controls with normal antenatal Doppler parameters matched for GA, birth weight, sex and year of birth. The main observation was that of all outcome parameters, the MDI in AREDF infants deviated by >1 SD from the test norm, and was significantly lower than in controls. The difference remained significant after adjusting for confounders that differed significantly between the groups, namely antenatal corticosteroids, SGA and maternal age.

Together with earlier reports,[8 30] this indicates that abnormal antenatal Doppler parameters might be an independent predictor of adverse neurodevelopmental outcome in preterm

Table 1 Sociodemographic, antenatal and neonatal characteristics of AREDF infants and controls

Characteristics	AREDF infants n=41	Controls n=41	p Value*
Sociodemographic			
SES total, median (range)	6.0 (3.0–12.0)	5.0 (5.0–12.0)	0.30
Maternal age, median (range), years	35.0 (27.0–51.0)	40.0 (32.0–52.0)	0.01
Number of siblings, median (range)	1.5 (1.0–4.0)	1.0 (1.0–4.0)	0.55
Caucasian ethnicity†, n (%)	33 (80%)	36 (88%)	0.56
Antenatal			
Preeclampsia, n (%)	10 (24)	19 (46)	0.06
Chorioamnionitis, n (%)	0 (0)	5 (12)	0.05
Caesarean section, n (%)	41 (100)	35 (85)	0.05
Reverse end-diastolic flow in UA, n (%)	6 (15)	–	–
Antenatal corticosteroids, n (%)	31 (76)	21 (51)	0.04
Neonatal			
Gender, male, n (%)	22 (54)	21 (51)	0.10
Gestational age, median (range), weeks	30.2 (24.9–35.0)	29.7 (25–35.5)	0.16
Birth weight, median (range), g	915 (400–1460)	1005 (620–1450)	0.07
Small for gestational age	27 (66)	15 (37)	0.01
Head circumference, median (range), cm	25.4 (21.0–29.5)	26.6 (21.5–31.0)	0.31
Apgar at 5 min, median (range)	7.0 (2–10)	7.0 (3–10)	0.85
Umbilical artery pH, median (range)	7.30 (7.08–7.38)	7.32 (7.05–7.42)	0.56
CRIB score, median (range)	4 (0–11)	2 (0–11)	0.28
Respiratory distress syndrome, n (%)	34 (83)	35 (85)	1.00
Mandatory ventilation, median (range), days	1.6 (0–18)	1.7 (0–12)	0.15
Bronchopulmonary dysplasia, n (%)	4 (10)	3 (7)	1.00
Sepsis, n (%)	5 (12)	5 (12)	1.00
Major brain injury, n (%)	2 (5)	2 (5)	1.00
ROP >stage 2, n (%)	2 (5)	0 (0)	0.15

*χ^2, independent t test or Mann–Whitney U test.
†Other ethnicities: Hispanic, Asian, Black.
AREDF, absent or reverse end-diastolic flow; CRIB, clinical risk index for babies;[38] ROP, retinopathy of prematurity; SES, socioeconomic status;[26] UA, umbilical artery.

Table 2 Outcome characteristics of AREDF infants and controls at age 20 months

	AREDF infants n=41	Controls n=41	p Value*	Adjusted p value†
Age at assessment, months, median (range)	23.0 (10.1–26.0)	23.5 (15.0–29.6)	0.92	–
Weight at assessment, kg, median (range)	10.6 (9.4–11.6)	10.9 (9.1–14.7)	0.79	–
Length at assessment, cm, median (range)	80.5 (77.5–84.4)	81.0 (76.4–93.0)	0.79	–
Head circumference at assessment, cm, median (range)	47.0 (42.7–49.0)	47.2 (46.0–51.5)	0.98	–
Neurodevelopmental outcome				
MDI, median (range)	84 (49–116)	91 (62–140)	0.005	0.03
PDI, median (range)	84 (49–117)	88 (50–112)	0.18	0.25
MDI <70, n (%)	10 (24%)	2 (5%)	0.01	0.004
PDI <70, n (%)	15 (37%)	8 (19%)	0.08	0.09
Cerebral palsy, n (%)	2 (5%)	3 (7%)	1.00	0.40
GMFCS level 1, n (%)	1	3		
GMFCS level 2, n (%)	1	0		
Minor neuromotor dysfunction, n (%)	20 (49%)	18 (44%)	0.82	0.78
Visual problems, n (%)	5 (12%)	3 (7%)	0.71	0.46
Hearing problems, n (%)	2 (5%)	0	0.23	0.78
Physical or occupational therapy, n (%)	15 (37%)	13 (32%)	0.49	0.64

Bayley scales of infant development, 2nd edition.[26] MDI and PDI <70, that is, <−2 SD from index norm 100. AREDF MDI mean (SD): 81.8 (16.3) and controls MDI mean (SD): 92.4 (16.3), AREDF PDI mean (SD): 81.3 (18.1) and controls PDI mean (SD): 86.4 (18.1). GMFCS[28] level ranging from 0 (normal) to 5 (most impaired).
*Independent t test or Fisher's exact test.
†Adjusted for antenatal corticosteroids, small for gestational age status (birth weight <10th centile), and maternal age (years).
AREDF, absent or reverse end-diastolic flow; GMFCS, gross motor function classification system; MDI, mental development index; PDI, psychomotor development index.

infants. This could be explained by impaired perfusion in AREDF infants compromising the conditions for intrauterine brain growth and development: despite an increase in brain perfusion, the circulatory impairment may be such that it induces a decrease in brain growth, with inevitable repercussions on early neurodevelopment. As reported in the fetal sheep,[31] an increase in placental impedance, reflected by abnormal UA Doppler parameters, is associated with abnormally low brain weight at birth and delayed neurodevelopment. Impaired microstructural brain maturation and metabolism is also related to neurodevelopmental outcome in very preterm infants,[32] while brain volume is reduced in infants with an abnormal UA:MCA pulsatility index ratio.[33]

Other studies on pathological antenatal Doppler flow used less robust matching criteria with an increased UA resistance index >95 percentile instead of UA AREDF (8; 33) or smaller sample sizes with UA AREDF[30 34 35] or included no control group,[33] but showed also that pathological antenatal Doppler flow is associated with unfavourable cognitive outcome, but not with motor development in former VLBW infants at 2 years of age.[33 34] Another study that compared only 16 very preterm infants with UA AREDF to GA-matched eutrophic controls found higher rates of mental delay and a tendency to more frequent motor problems at age 2 years, which was not surprising.[35] Our study, however, matched 41 children to the GA and also to the birth weight and detected a worse mental development of children with AREDF.

Table 3 Multivariate regression analyses for predictors of mental and psychomotor development indices (Bayley scales of infant development, 2nd edition)[26] in the study subjects

	Mental development index*				
	B	SE	β	T	p Value
AREDF	−8.35	4.13	−0.25	−2.02	0.048
Gestational age	1.07	1.21	0.11	0.88	0.38
SES total	−1.57	0.95	−0.20	−1.66	0.10

*F=3.50, p=0.02, R2=0.15, R2 adjusted=0.11.
AREDF, absent or reverse end-diastolic flow; SES, socioeconomic status.[26]

The strengths of this study are fivefold: good determination of GA using early ultrasound; comparison with a control group matched for sex, GA, birth weight and year of birth; highest sample size of children with UA AREDF with 2-year follow-up reported in literature; longitudinal follow-up of VLBW subjects and standardised same-centre neurodevelopmental assessment. The criteria used for matching the control group enabled us to consider UA AREDF as an independent risk factor for adverse neurodevelopmental outcome. Because of the association between pathological UA Doppler parameters and IUGR,[7] AREDF infants tended to be lighter at birth than controls. Chorioamnionitis, which has been associated with adverse long-term outcome in preterm infants,[36] tended to be more frequent in controls, as others have noted.[35 37] A possible explanation is that the pregnancies complicated by AREDF in our study were likely to have been more intensively monitored than those in the control group. The same explanation may account for the lower exposure to antenatal corticosteroids in controls.

The main limitations of the study are its retrospective design. Additionally, even though our study has the highest sample size reported in the literature compared with similar studies, the power of the analysis might have been decreased through the high loss to follow-up. Another limitation is that the study infants were young enough at outcome assessment for a difference in CP rate to become observable at a later stage. Prospective outcome assessment into adolescence or early adulthood is definitively required in larger cohorts of infants with abnormal UA Doppler parameters in order to better analyse the long-term impact of AREDF on neurodevelopment and social functioning.

In conclusion, we found that VLBW infants with UA AREDF are at higher risk of poorer mental development at median 23.3 months' CA than controls matched for GA, birth weight,

sex and year of birth. Our finding suggests that UA AREDF is an independent predictor of poorer mental development in this population. More data and longer-term follow-up are required to eliminate SGA bias and better evaluate the impact of UA AREDF on later neurodevelopment.

Contributors SB, NO-K and GN had primary responsibility for the study design, data acquisition, data analysis and writing the manuscript. TB was involved in data analysis and data interpretation and writing of the manuscript. JK, DB and RZ were involved in study design, data acquisition and in revising the manuscript. All authors approved the final version of this manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Local Cantonal Ethics Committee of Zurich, Switzerland.

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Data sharing statement Dataset is available from the corresponding author who will provide a permanent, citable and open access home for the dataset.

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